REMARKS

Applicants would first like to thank Examiner Shin and Primary Examiner Angell for their time and helpful suggestions during the telephonic interview with the undersigned and one of the inventors, Dr. James Donegan on November 17, 2008. During the interview, the pending claims and prior art were discussed. The substance of the interview is provided below.

Claims 275, 289-290 and claims 296-301 are pending in the current application; claims 298-301 have been withdrawn. Claim 275 has been amended to more distinctly claim that which Applicants regard as the invention. Applicants reserve the right to file subsequent continuation/divisional applications to subject matter originally recited in claim 275. The claim amendments will be discussed in further detail below.

I. SUBSTANCE OF INTERVIEW

A. Brief Description of any Exhibit Shown or any Demonstration Conducted

Applicants submitted Figures 22 and 23 of the specification since these figures were used in distinguishing the claimed invention from the prior art.

B. Identification of Claims Discussed

Claim 275 was discussed.

C. Identification of Specific Prior Art Discussed

As will be set forth in further detail below, Ekwuribe et al., US Patent No. 5,438,040 was discussed with respect to the rejection under 35 USC 112 and Ryser et al., US Patent No. 4,847,240 and Wu et al., US Patent No. 5,166,320 was discussed with respect to the rejection under 35 USC 103

D. Identification of Principal Proposed Amendments of a Substantive Nature Discussed

Amendments to claim 275 were discussed.

E. Identification of General Thrust of Principal Arguments presented to the examiner

Undue experimentation would not be involved in obtaining the claimed composition. The claimed compositions are not obvious over the cited prior art.

F. A General Indication of Any other Pertinent Matters Discussed

No other pertinent matters were discussed.

G. General Results or Outcome of the Interview

Applicants will in the written response present the amendments and arguments made during the interview.

II. The Rejection Under 35 U.S.C. §112, First Paragraph

Claim 297 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Office Action specifically states:

> The claim is drawn to a multimeric complex composition of multiple monomeric units of insulin that are covalently attached to one another.
>
> Throughout the entire disclosure of the specification, there is only one occurrence where a single "potential" utility for the claimed multimeric complex of insulin is indicated such that it "could be useful in that manner in diabetic treatment". See page 78. In addition, the specification is devoid of any working example demonstrating that the claimed composition of claim 297 is indeed useful in diabetic treatment. Contrary to the prophetic teaching that the claimed multimeric complex of insulin is useful for diabetic treatment, covalent insulin dimers were specifically warned against being used in diabetic treatment at the time of the invention. For example, Ekwuribe (US 5,438,040) teaches that insulin has been used as a therapeutic drug for diabetes since 1922. See column 4, lines 4-13. Ekwuribe teaches that "There is significant evidence that the incidence of immunological responses to insulin may result from the presence of covalent aggregation of insulin in blood of insulin-using diabetic patients." See column 5, lines 44-49. In addition, Ekwuribe teaches that as many as 30% of diabetic subjects receiving insulin show specific antibodies to "covalent insulin dimers" and therefore it is recommended

that the covalent insulin dimer content is maintained below 1%. See column 5, lines 57-66.

Given the specific teachings against increasing covalent insulin dimer content and the art recognized recommendation for making insulin products that are low in the covalent insulin dimer content for diabetes treatment, the instantly claimed multimeric insulin composition is considered to lack the asserted utility as a diabetes therapeutic composition. Since the prior art reference of Ekwuribe taught away from the claimed composition, in particular with regard to the single asserted therapeutic utility in a diabetes treatment regimen, a person skilled in the art would not have been able to make the claimed multimeric composition of insulin and use it in a diabetes treatment method as suggested by the specification. Furthermore, the specification does not disclose any factual evidence that the claimed multimeric composition of insulin could work as a diabetes treatment drug as asserted in the specification.

Since the specification fails to adequately describe how to use the invention as a diabetic therapeutic composition as stated in the specification, despite the art-recognized counsel against the use of covalent insulin dimers, it is concluded that the claimed invention for diabetes treatment is not enabled at the time of the invention and that one of ordinary skill in the art would not have made and used the claimed composition without undue experimentation at the time of the invention.

Applicants respectfully traverse the rejection. The Office Action takes the position that bringing multiple copies of insulin together is intrinsically harmful ("covalent insulin dimers were specifically warned against") and makes a reference to antibodies in Ekwuribe against "covalent insulin dimers". The "covalent dimers" are not the equivalent of the multimers of the present invention. The linking together of two insulin molecules by a rearrangement of the disulfide bonds generates a chimeric epitope that brings together domains from individual insulin molecules that would never be in proximity to each other in a single protein. Thus the juxtaposition of a few amino acids from one insulin molecule and a few amino acids from a second insulin molecule presents a surface that looks like a new or foreign protein.

For example, consider a hypothetical situation where part of a protein consists of ------Glu-Glu-Glu-Met-His-Arg-Ser-Ser------ and another section of the same protein

consists of the sequence --------Thr-Leu-Glu-Met-Arg-Arg-Arg------ . Due to folding considerations, these sequences are spatially separated into different domains and each of the Met resides is involved in different internal disulfide bonds. If there is a transformation where these disulfide bridges are broken and a crosslinking event takes place between two different proteins, there is a situation where a sequence on a surface could be represented as:

Glu-Glu-Glu-Met-(S-S)-Met-Arg-Arg-Arg-Arg-

which immunologically speaking results in a new epitope that is not found in the native protein. Thus it is understandable that covalently linked dimers of insulin can invoke immunological responses.

In contrast, the present invention, does not involve such intimate crosslinking such that domains on different proteins are brought into such permanent close proximity. The nucleic acid that is used for creation of protein/nucleic acid monomers of the present invention serves as a linker that can be used for multimerization but it does not create new epitopes derived from fusion of two protein sequences into a chimeric sequence. The present invention does not involve such intimate repositioning of protein domains from separate insulin molecules; nucleic acids are used for the linkages, thereby providing a length between individual insulin molecules much longer than the extremely short S-S bonds involved in formation of covalent insulin dimers. Consequently, the surfaces of the insulin monomers will look normal to the immune system and should not invoke any particular antibodies.

In view of the above arguments, Applicants assert that the rejection under 35 USC 112, first paragraph has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

5. The Rejection Under 35 USC 103

Claims 275 and 296-297 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ryser et al. (US 4,847,240) in view of Wu et al. (US 5,166,320). The Office Action specifically states:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the supramolecular composition structure of Ryser et al. by

replacing the covalently-binding poly amino acid (PAA) with the covalently-binding polynucleotide of Wu et al., thereby producing a multi-complex of hormones covalently linked via polynucleotides.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success, because Ryser et al. taught that protein hormones or polypeptide hormones, such as insulin, can be more efficiently delivered into target cells when the protein hormones are covalently bound to polymers such as a poly amino acid (PAA) in soluble form, thereby forming a supramolecular structure, and because Wu et al. taught the carrier system structure comprising a polynucleotide (a polymer) that is covalently attached to a ligand for a protein receptor for delivering the polynucleotide into target cells. Since the use of polymers for covalently conjugating or attaching to protein hormones or ligands for protein receptors with a resultant effect of enhanced cellular uptake of the protein hormones was known in the art, one of ordinary skill in the art trying to increase the efficiency of cellular uptake of protein hormones or ligands for protein receptors would have been motivated to conjugate them to a polymer such as a polynucleotide or a poly amino acid, which covalently binds to the protein/ligand molecules. Further, one of ordinary skill in the art desiring to deliver more than one unit of protein hormone or ligand in a simultaneous manner would have been motivated to covalently attach each protein/ligand to make a multimeric compound comprising multiple units of protein hormones or ligands, by utilizing the inherent property of polynucleotides that hybridize with complementary nucleotide sequences as depicted by Wu et al. Since the utility of polymers as carriers for hormones (e.g., insulin) was known in the art as taught by Ryser et al., and since the polynucleotide carrier system structure comprising a ligand for a protein receptor linked to a polynucleotide was known in the art as taught by Wu et al., one of ordinary skill in the art would have had reasonably arrived at the claimed multimeric composition at the time of the invention. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Applicants respectfully traverse the rejection. Before, responding to the rejection, Applicants note that claim 275 has been amended to recite that the protein is covalently bound to a single-stranded polynucleotide to form a monomeric unit; each monomeric

unit is attached to a binding matrix (a polynucleotide comprising sequences complementary to the single-stranded polynucleotide of the monomeric unit).

With reference to page 6 of the Office Action, Applicants would disagree that the invention becomes obvious with the combination of Ryser and Wu. Ryser actually teaches a protein attached to a cationic polyamino acid. In particular, in Ryser, the protein is covalently attached to the polyamino acid in optimally several places to form a conjugate. Therefore, a polymeric composition is formed once the protein binds to the polymeric amino acid. The conjugate is subsequently taken up by the cell and electrostatic bonds are formed between the polyamino acid and proteins in the cell. Thus, in Ryser, a multi-ligand conjugate is formed before there is any binding of a nucleic acid. In contrast, in the composition of the present invention, only monomeric units are formed when the protein binds to the single-stranded polynucleotide. Polymeric units are not formed until the monomeric units are attached to the binding matrix.

Applicants note that in Wu et al., the polynucleotide does not function as a matrix to bring individual monomeric units together. The DNA is actually separated from the protein monomers by polyamino acid cation. The DNA in the composition of Wu is not being used for the purpose of acting as a matrix. Instead, it is the material that is being taken up by the cell.

In summary, Ryder and Wu actually share a feature that is differentiated from the present invention, the matrix that binds the individual monomers together in both of these disclosures are polycations such as polylysine, i.e., a polypeptide. Although as noted above, a polynucleotide is used in Wu, it does not function as a matrix to bring individual monomeric units together. Applicants also disagree with the statement in Page 8 that "Wu et al., taught the carrier system comprising a polynucleotide (a polymer) that is covalently attached to a ligand....." It can be clearly seen in the illustration that is provided in the Office Action that there is no covalent attachment between the polynucleotide and the ligands. Rather there is electrostatic binding between a polycationic polymer and a DNA molecule. Furthermore the abstract itself states: "The soluble DNA-carrying complex is formed by non-covalently binding a ligand conjugate with the foreign gene." (emphasis added). The DNA in the illustration

in Wu clearly does not function as a matrix bringing the monomeric units together as recited in claim 275. Instead, the opposite function is being served in that a cationic polymer is used to create a multimer and this preformed multimeric is then used to bind a DNA molecule. There is also a critical difference in that claim 275 as amended requires the use of a protein that is covalently attached to a nucleic acid, an element that is completely missing in both the Ryser and the Wu references.

Applicants assert that the multimeric composition of the present invention would not be obtained even if Ryser and Wu were combined. In both of these disclosures, multiligands are preformed before they are ever bound to a DNA molecule. In addition, both Ryser and Wu describe the use of a polycation to bind ligands together into a multimer and the DNA used in the present invention for multimerization is actually a polyanion.

Claims 296 and 297 depend from claim 275. Thus, arguments made with respect to claim 275 would also apply to claims 296 and 297.

In view of the above arguments and the amendment of claim 275, Applicants assert that the rejection under 35 USC §103 has been overcome. Therefore, Applicants respectfully request that the rejections under 35 USC §103 be withdrawn.

SUMMARY

It is Applicants belief that the pending claims are in condition for allowance. If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,

/Cheryl H Agris/

Date: November 28, 2008 Cheryl H. Agris, Reg. No. 34,086